Antimicrobial peptides: an alternative to antibiotics?

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BACKGROUND AND OBJECTIVES

- WHO has declared that AMR (Antimicrobial Resistance) is one of the top ten biggest threats to global health, food security and development today.

DRIVERS: Use of antimicrobials; Cross-transmission

HOW OCCURS: Acquirement of antibiotic-resistant genes; Spontaneous mutations in DNA; Transfer from one bacteria to another

CAN AFFECT: Anyone; Any age; Any country

700.000 people die each year worldwide

- The **aim** of this review is to expose an insight into the suitability of the use of antimicrobial peptides as an alternative to antibiotics in the treatment of *S. aureus* infections, one of the most commonly bacteria developing AMR.

FEATURES AND PROPERTIES OF AMPs

Broad Description

- Cationic and amphipathic.
- Encoded in genes and synthetized by ribosomes.
- The most common structures are helical and β-sheet rich AMPs.

Mechanism of action

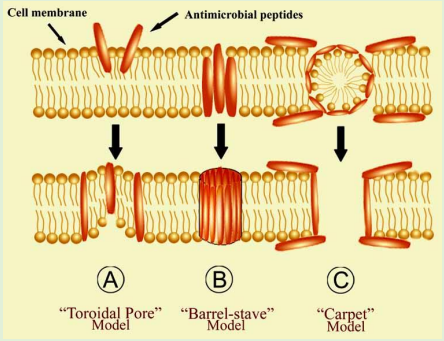

***Figure 1**. Models explaining the different membrane permeabilization mechanisms of AMPs. Retrieved from [4].*

Less proneness to resistance development

- Membrane disintegration is energetically unfavourable.
- Distinct lipid composition and neutral charge of eukaryotic membranes compared with bacterial ones, leads to a different kinetics of AMP interaction.

Outstanding properties and objections

Broad-spectrum activity and fast rate of killing	Extensive and costly large-scale production
Additional anti-inflammatory properties	Susceptible to proteolytic degradation
Less prone to develop resistance	Can be toxic at high concentrations
Therapeutic and antimicrobial activity at low concentrations	Unknown pharmacokinetics

APPLICATION AND THERAPEUTIC USES

Cit 1.1

- AMP from the skin glands of *Litoria citropa*.
- Antimicrobial activity against MRSA through carpet model mechanism.

Temporins

- AMPs from amphibian skin glands.
- Membranolytic action against some *staphylococci* strains. Also towards dormant cells.

Serine-protease Esp

- The presence of *S. epidermidis* in the nasal cavity correlated with the absence of *S. aureus* colonization.

Staphylococcins

- Action against strains closely phylogenetically related or within the same niche as the producer.
- The majority of them belong to **lantibiotics** class.

- Nisins
- Epidermin
- Microbisporcin (NAI-107)
- Lacticin Q
- Nukacin ISK-1
- Pep5

AMPs with anti-biofilm capacity

They interfere in various stages of biofilm-formation:

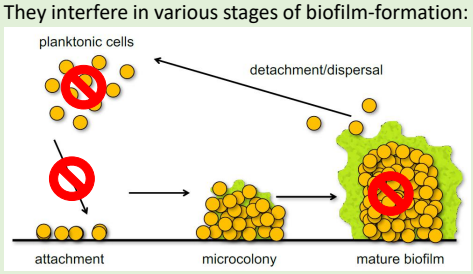

***Figure 2**. The biofilm life cycle and action of anti-biofilm AMPs. Adapted from [5].*

- Nisin A
- Temporin G
- Epidermin
- Esp
- Lysostaphin

- **DJK-5** → it does not target metabolically-active bacteria, but promotes degradation of (p)ppGpp

AMPs with wound-healing promoting activity

Involved in tissue regeneration

Examples: AG30/5C, WRL3 and Epinecidin-1

OPTIMIZATION STRATEGIES

1. INCREASE STABILITY

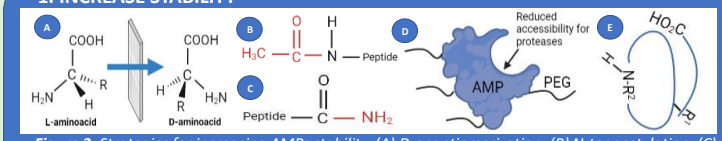

***Figure 3**. Strategies for increasing AMPs stability. (A) D-enantiomerization; (B) N-ter acetylation; (C) C-ter amidation; (D) Pegylation; (E) Peptide Cyclisation*

2. DELIVERY STRATEGIES → Topical therapy is preferred

Nanotechnological platforms and scaffolds | Increased aqueous solubility and moderate lipophilicity | Peptide cyclisation | Penetration enhancers | <500 Da

3. IMPROVE ACTIVITY AND POTENCY

Amphipaticity
Hydrophobicity
Net charge

AMPs + Antibiotics

Other combinations:
- AMP +antibiotic-resistant breakers
- AMP+EPS-inhibiting agents
- AMP+chelating agents
- AMP+matrix disagreggating agents

4. REDUCE TOXICITY

Short AMPs → poor immugenicity but reduced antimicrobial activity

Possible options:
- D-enantiomerization
- Switching polar to non polar residues

CONCLUSIONS AND FURTHER DIRECTIONS

- The most important factors that make AMPs promising candidates as antibiotic alternative are the **broad-spectrum** of activity, the **low proneness to resistance development** and their **anti-biofilm activity**.
- Although propitious candidates are emerging with synthetic methods, **toxicity and high-production cost are still hurdles to deal with**.
- **AMPs in combination with antibiotics** seems to be a viable and transient solution until more sophisticated achievements are reached.

- **Structure-function studies** may provide relevant information to overcome host toxicity of AMPs.
- Novel approaches for **peptide synthesis based on innovations in synthetic biology** may open the door for easier and cost-effective production.

REFERENCES

[1] Pfalzgraff A, Brandenburg K and Weindl G. (2018). Antimicrobial Peptides and Their Therapeutic Potential for Bacterial Skin Infections and Wounds. *Front. Pharmacol., 9*,1-23.
[2] Luong, H. X., Thanh, T. T., & Tran, T. H. (2020). Antimicrobial peptides - Advances in development of therapeutic applications. *Life sciences, 260*, 118407.
[3] Ciandrini E, Morroni G, Arzeni D, Kamysz W, Neubauer D, Kamysz E, Cirioni O, Brescini L, Baffone W, Campana R. (2018). Antimicrobial Activity of Different Antimicrobial Peptides (AMPs) Against Clinical Methicillin-resistant Staphylococcus aureus (MRSA). *Curr Top Med Chem., 18*(24),2116-2126.
[4] Meng S, Xu H, Wang F. (2010). Research advances of antimicrobial peptides and applications in food industry and agriculture. *Curr Protein Pept Sci., 11*(4),264-273.
[5] Mansour, S. (2018). A novel peptide-based treatment for bacterial abscess infections- PhD Thesis. *University of British Columbia Library*.